Fetal Surgery: Trials, Tribulations, and Turf

Michael R. Harrison, M.D.
Professor of Surgery, Pediatrics, and Obstetrics, Gynecology & Reproductive Sciences
Director, Fetal Treatment Center
Division of Pediatric Surgery, Department of Surgery,
University of California, San Francisco

Introduction

Although it is now clear that the fetus has become a patient whose maladies deserve treatment, it is not yet clear what role fetal surgery plays now and will play in the future. Opinions vary about the state of fetal surgery in 2002, ranging from unrealistically optimistic (all birth defects will be diagnosed and treated before birth) to outright skeptical (a lot of "hype" over unproven treatment for rare disorders). I will attempt to provide some perspective by addressing three questions: 1) What diseases are treatable and how have we done in treating them to date? (a report card on fetal surgery 2002); 2) Who is the fetus's doctor? (obstetrician, neonatologist, surgeon) 3) How should the care of the fetus be organized? (the role of centers, professional groups, and trials).

How the Fetus Became a Patient in Our Lifetime

It is important to recognize that it is only during our professional lifetime, the last decades of the 20th century, that the fetus has become a patient (Table 1). Only recently have powerful new imaging and sampling techniques stripped the veil of mystery from the once secretive fetus. Although most prenatally diagnosed malformations are best managed by appropriate medical and surgical therapy after maternal transport and planned delivery near term, a few simple anatomic abnormalities with predictable devastating developmental consequences will require treatment before birth.

Beginning in the early 1980s, the developmental pathophysiology of several potentially correctable lesions was worked out in animal models; the natural history was determined by serial observation of human fetuses(1-3); selection criteria for intervention were developed(4-9); anesthetic and tocolytic regimens were refined(10,11); surgical techniques for hysterotomy and fetal repair were developed and refined(12,13); and finally minimally invasive techniques for fetal intervention (Fetendo) were developed and refined(14,15). A subjective listing of milestones provides an overview of this history (Table 1). This investment in basic and clinical research has benefited an increasing number of fetal patients with a few relatively rare defects, and will benefit many more as new forms of therapy including stem cell transplantation, tissue engineering, and gene therapy are applied to a wide variety of anatomic and non-anatomic defects detected before birth.

More recently, indeed within the last 10 years, three important trends in fetal therapy have emerged; all three are illustrated by the evolution of fetal treatment for severe congenital diaphragmatic hernia (CDH). The first is a movement away from total surgical repair of the anatomical defect (diaphragmatic hernia) and toward manipulation of the physiology of lung development(14). For example, when complete repair of the anatomical defect via open fetal surgery proved technically impossible for fetuses with liver herniation , and unnecessary for those milder cases without herniated liver, it spurred the development of a physiology-based strategy aimed at inducing lung growth by preventing the normal egress of fetal lung fluid(16,17).

A second trend in fetal therapy is from open fetal surgery via hysterotomy to minimally invasive surgery using small trocars and a combination of videofetoscopic and sonographic visualization. For example, the need for reversible temporary tracheal occlusion spurred the development of minimally invasive surgical techniques: first, the Fetendo clip procedure and now the Fetendo balloon technique(15,18). Significant technical problems had to be overcome in performing Fetendo surgery including development of

appropriate small trocars and dissecting instruments, development of a continuous perfusion hysteroscope so that procedures could be performed in the native fluid environment of the fetus rather than the usual CO_2 gas environment, and development of positioning and fixation techniques for the free-floating fetus. Successful placement of a detachable tracheal balloon through one fetobronchoscopic port is the latest advancement in this continuing trend to less and less invasive fetal intervention.

A third trend in fetal therapy is from case histories and registries to randomized controlled trials to establish the safety and efficacy of new fetal procedures. For example, the first CDH trial stopped open fetal repair of CDH, and a second trial will establish the place of temporary tracheal occlusion(19).

Fetal Surgery Report Card 2002

Rather than present a vast amount of information on a growing number of fetal diseases and their treatment (all covered extensively in 3rd Edition of *The Unborn Patient: The Art and Science of Fetal Therapy*)(20), I have attempted to summarize the state of the field by assigning an admittedly subjective grade to our collective efforts to treat each fetal disease. Like school report cards, each aspect of treatment is graded on a scale "A" to "F" including our understanding of the pathophysiology of the process and, thus, rationale for treatment, the natural history of that disease in the human fetus and our ability to select the appropriate fetus for treatment based on severity of the process, and finally a grade for the various types of intervention ranging from the minimally invasive, percutaneous, sonographically-guided interventions through fetoscopic or (Fetendo) interventions with or without maternal laparotomy, and finally to open fetal surgery by hysterotomy. The report card for 2002 is presented in Table 2.

The Fetus's Physician(s)

It is clear from the historical development of fetal treatment that the fetus with an anomaly requires the attention of a team of specialists working together. Management of the defective fetus does not easily divide according to the sometimes artificial (and negotiable) time of delivery. Whether the patient is inside or outside the womb, its care is a continuum that requires the expertise of physicians trained in the care of mothers and babies. It is hard to imagine how one specialist, no matter how broadly trained, could take sole responsibility for the treatment of a fetus with a complex malformation.

The obstetrician will manage the pregnancy. The obstetric specialist (e.g., perinatologist, geneticist) who is an expert in prenatal diagnosis, amniocentesis, chorionic villus sampling, percutaneous umbilical blood sampling, and so forth, is indispensable in fetal diagnosis, family counseling, and management of the pregnancy and its complications. But he or she is rarely familiar enough with management of the neonate's disease process after birth to make decisions about exactly how it should be managed before birth. By the same token, the neonatologists or pediatric surgical specialist familiar with the disease process, its pathophysiology, and its treatment after birth, although indispensable in formulating treatment, and in some case, performing the surgery, is not qualified to manage the pregnancy or the obstetric problems associated with intervention. In addition to physicians trained in the clinical care of the pregnant woman and the newborn with a defect, the expertise of other specialists is often required, e.g., obstetric sonologists experienced in prenatal diagnosis, pediatric cardiologists experienced in treating arrhythmias, neurosurgeons experienced in treating myelomeningocele, and psychosocial professionals experienced in counseling, etc. The process by which families are educated and counseled about their options is crucial. To avoid misunderstanding, joint counseling sessions with different team members providing input to the family in the presence of other disciplines is preferable to a series of meetings with each discipline.

Who Does What in Fetal Intervention: Principles

A special problem arises with interventional fetal procedures, especially those that require the expertise of specialists from very different fields. For example, who should place vesicoamniotic shunts: the obstetrician expert in percutaneous sonographically-guided fetal sampling and manipulation, or the pediatric surgical specialist expert in catheter drainage of obstructed urinary tracts in infants? Who should perform open fetal surgical procedures: the obstetrician experienced in uterine surgery, or the pediatric surgeon experienced in repair of complex anomalies in very small children? Because no single specialty training provides the total spectrum of skills and experience, this is an area in which "turf" battles between medical specialties and "ego" battles among team members may sabotage the fetal treatment enterprise. However, it is also an area in which cooperative efforts and teamwork can be very productive.

Although there is no simple solution to this problem, some general principles have evolved during the last decade in centers in which obstetricians, sonologists, surgeons, and many other specialists have been working closely together to improve fetal treatment (Table 3). The first principle is that fetal therapy is a team effort requiring varying amounts of input from all team members. The team must include an obstetrician or perinatologist, geneticist, sonologist, surgeon, neonatologist, anesthesiologist, and many other support personnel. This range of expertise can usually be provided by three or four individuals, depending on what roles are combined; that is, an obstetrician, a sonologist, a surgeon, and an anesthesiologist.

The second principle is that although all members of the team can contribute to any particular procedure, there must be a team leader who takes responsibility for the conduct of that particular procedure. Which member of the team becomes the leader depends on the nature of the procedure itself (Figure 2).

The third principle is that the procedure is done by the team member who is most likely to produce the best outcome. For example, if fetal outcome depends on skill and expertise in performing sonographically-guided percutaneous procedures, the obstetrician/sonologist is usually in charge of the team and performs the procedure. For open surgical procedures, the roles are reversed because the outcome is related directly to the skill, judgement, and experience of the surgeon. The risks for mother and fetus are higher than are those for closed procedures, and success depends on the ability of the surgeon to expose the fetus by hysterotomy, correct the defect, return the fetus, and close the still-pregnant uterus securely.

Although open fetal surgical procedures constitute a small minority of the procedures performed, the problem of who should lead the team and who (or how many) should perform the procedure deserves thoughtful consideration. The simplest solution is to ask each surgical specialist to do his or her part of the procedure; that is, the obstetrician opens the uterus, the pediatric surgical specialist (e.g., pediatric surgeon for lung resection, pediatric neurosurgeon for myelomeningocele) operates on the fetus, and the obstetrician closes the uterus. Although this politically expedient solution is the easiest way to approach fetal surgery and is likely to keep team members comfortable in their accustomed roles, it is not likely to yield the best outcome for several reasons. This approach assumes that traditional skills will suffice; that is, the obstetricians can close the still-pregnant uterus as they do in the case of an empty uterus and that the pediatric surgeon can do with a fetus what he has learned in a neonate. Neither is true. Second, tag-team surgery is never ideal. Exposure of the fetus by hysterotomy or fetoscopy, positioning and stabilization of the fetus for the planned intervention, repair of the defect, and closure of the uterine incision or trocar sites are too intimately intertwined to be divided up by specialty "turf." The chance of success is highest when one physician takes responsibility for the procedure from the beginning to the end. Fetal surgery cannot develop and will not succeed unless a few surgeons are willing to devote considerable time and effort to developing, practicing, and perfecting all aspects of this new procedure: fetal exposure by hysterotomy and/or fetoscopy; correction of a wide variety of fetal defects; closure of the pregnant uterus; and postoperative surgical and tocolytic management.

3 Ways to Get "Mother Doctors" and "Baby Doctors" Working Together

Although specialists in fetal therapy could emerge from a variety of backgrounds, including surgery, obstetrics, sonography, interventional radiology, and prenatal diagnosis, most invasive and truly surgical procedures will be performed by individuals who have been prepared either in a pediatric surgical or perinatology training program. Individuals who have trained in these programs have similarly extensive background and appropriate board-certification (Table 3). The principal problem is not the background, but that the cultures in the past have proven quite disparate, and it takes a good deal of effort to get talented individuals from these two disparate cultures to work closely together.

We have learned that there are three good ways to foster collaboration and teamwork. 1) The weekly fetal treatment meeting attended by all disciplines at which real problems in real patients are presented, discussed, argued, and resolved. 2) Ongoing laboratory research in which all disciplines participate, e.g., animal models of fetal diseases where intervention techniques are developed and teamwork practiced (e.g., Fetendo was developed and practiced in animals before being applied clinically). 3) Presenting clinical and research papers together at national meetings of each other's professional societies, e.g., pediatric surgeons presenting at the Society for Maternal-Fetal Medicine, or perinatologists at the American College of Surgeons or APSA. Unfortunately, so far there is only one professional common meeting ground, the International Fetal Medicine and Surgery Society (IFMSS), which was founded in 1982 as a forum for surgeons, perinatologists, neonatologists, physiologists, and many others to come together and share their work. The annual meeting is informal, stimulating, and open to all.

Fetal Surgery Centers: How Many and What Kind

Although the infrastructure (type and number of centers) and funding for fetal surgical care should be directly related to the projected need for fetal surgery, in our system, other factors, including institutional prestige, competition for patients and dollars, etc., will inevitably influence the outcome. Based on projected need over the next five to ten years, the number of centers would be quite limited (Table 4). For open or fetendo surgery, the number of cases will increase only a little over the next few years and may decline after that as other approaches develop. For the next few years, only myelomeningocele and twin-twin transfusion syndrome promise any significant volume, and both will be tied up in national randomized clinical trials for several years. The big unknown in open fetal surgery is myelomeningocele, which is by far the most prevalent, and could double or triple the number of open cases in the United States, if it is proved to be an appropriate treatment in the NIH-sponsored randomized controlled trial, which will begin this summer. The results will not be known for several years and, in the meantime, none of these cases can be done outside of the three centers performing the trial, thus limiting the development of new programs over the next few years.

The less invasive procedures will be performed more commonly, but can also be mastered by a broader group of practitioners who do not necessarily require a specialized center capable of open fetal surgery. Twin-twin transfusion is by far the highest volume procedure and, at present, requires tertiary/quaternary expertise. But, if the procedure is proven effective in an NIH-sponsored randomized clinical trial, that considerable volume would justify creation of more centers.

The number of centers will ultimately depend not only on the need, but also on what the centers should look like, and thus the degree of difficulty in creating these centers. There are three existent models, each with very different implications for how many centers will evolve. The first I will call the "Academic Multidisciplinary Model." This model developed 20 years ago at the University of California, San Francisco (UCSF) and has been replicated at the Children's Hospital of Philadelphia (CHOP). This resource-intensive model requires extensive clinical expertise in perinatology, neonatology, pediatric surgical subspecialties, genetics, prenatal diagnosis, anesthesia, etc., as well as a multidisciplinary fetal conference that meets weekly, active management of a large number of cases referred from great

distances, ongoing clinical research including participation in randomized clinical trials, extensive ongoing basic science laboratory research and collaboration with basic scientists in developmental biology, tissue engineering, stem cell biology, etc. It can almost certainly only be accomplished in a quaternary university medical center and requires considerable financial and administrative support as well as extramural research funding. This kind of Fetal Treatment Center will be limited to a small number of high-level university medical centers.

The second model I will call the "Perinatologist plus Surgeon Model," best exemplified by the program developed to treat myelomeningocele at Vanderbilt. In this model, a few dedicated perinatologists team with a specific surgical subspecialist to treat a specific disease (e.g., perinatologist plus neurosurgeon for repair of myelomeningocele). They develop a focused clinical unit, which includes supportive neonatologists, nurses, and administrators. They may perform some ad hoc laboratory research to develop a specific intervention. For surgical procedures, the perinatologist and surgical subspecialist each perform their part of the procedure in tandem: the obstetrician opens the uterus, the neurosurgeon repairs the defect as he would after birth, and the obstetrician closes the uterus. This model is considerably easier to implement because the individuals are performing their parts of the procedure as they are used to without having to cross-train or develop new skills. This would require the resources of a tertiary medical center and significant clinical revenue, but not necessarily extramural funding for research. Thus, this model could be easily replicated in a relatively large number of medical centers around the country that have a perinatologist and a surgical subspecialist interested in teaming up to treat a specific disease.

The final model I will call the "Virtuoso Model" in which a talented individual practitioner develops a reputation for treating a specific disease using new minimally invasive (often fetoscopic) techniques, the best example being the treatment of twin-twin transfusion syndrome in Tampa. This model requires only a well-known individual capable of attracting referrals and developing virtuoso minimally invasive fetoscopic procedures, which can sometimes be done in an outpatient or less intensive environment. It does not require, but may include, some animal research. It does not require development of a large team to perform the procedures. This model could potentially apply to any medical center with a virtuoso capable of attracting referrals and clinical revenue, and thus could be applied to literally hundreds of existing centers.

Which type of Fetal Treatment Center is best remains to be seen. In our pluralistic system, all may have a role, depending on need, institutional ambitions and resources, and perhaps, most important, the marketplace. At present, third party payors cover only a few procedures at a few centers. They are unlikely to expand coverage for new procedures at new centers unless they are shown to be effective and cost-effective in proper trials. Thus, trials will assume new importance in determining the future of fetal surgery.

The Maturation of Fetal Surgery: From Case Histories to Registries to Trials

New technologies usually start in a single, highly committed center, and initially remain confined to a relatively small number of centers with the interest, expertise, and resources to achieve reasonable results. Results are reported as case histories. This was fetal therapy in the 1980s. In the early phase, multicenter registries are often useful. Such was the case for the initial registries sponsored by the International Fetal Medicine and Surgery Society for cases of hydronephrosis and hydrocephalus treated with shunts.

As technologies like fetal surgery diffuse out to other developing fetal centers, the value of multicenter registries and non-randomized trials decreases. Such proved to be the case in the late '80's and early '90's for attempted registries for fetal metabolic diseases and cardiac arrhythmias, and attempted trials for management of gastroschisis and urinary tract obstructions.

In the last decade, it became clear that for fetal therapy to progress it would be necessary to determine the efficacy of intervention through properly controlled clinical trials; but proper trials have proven incredibly difficult to execute. Two multicenter trials comparing vaginal to Cesarean delivery for gastroschisis have

not succeeded despite considerable effort. A European multicenter trial on twin-twin transfusion syndrome has stalled. Single-center trials are much easier logistically. The only successfully completed controlled trial of fetal therapy to date is the UCSF trial comparing open repair of CDH to repair after birth. Despite incredible logistic and bureaucratic challenges, this trial showed that open surgical repair of fetal diaphragmatic hernia was no better than treatment after birth, prevented further attempts at open repair of diaphragmatic hernias around the world, and directly spurred development of a physiologic approach to reversing pulmonary hypoplasia by temporary tracheal occlusion. If demonstrated, the power of properly conducted clinical trials in establishing practice patters, determining future directions, and even deciding payment for new procedures. The power of trials is now being brought to bear on at least two other dilemmas in fetal therapy: open surgical repair of myelomeningocele and laser ablation of placental vessels for TTTS.

The short but eventful history of the fetus as a patient reassures us that fetal treatment offers new hope for the fetus with a correctable defect, and reminds us that there is considerable potential for doing harm. We know that innovative fetal treatment must be fully tested in the laboratory, carefully considered in the light of current diagnostic and therapeutic uncertainties, honestly presented to the prospective parents, and finally undertaken only with trepidation. It is now clear that because a procedure can be done does not mean that it should be done and that a fetal abnormality of any type should never be treated simply "because it is there," and never by someone who is unprepared for this fearsome responsibility. In the early harrowing days of fetal treatment, no one could be sure whether the enterprise would succeed or die. We can say the enterprise has succeeded now that the fetus is a patient, that the fetal patient has a doctor, and in some cases that the fetal patient has a surgeon. Fetal therapy as an enterprise has succeeded with its own society (the Fetal Medicine and Surgery Society), its own journal (*Fetal Diagnosis and Therapy*), and successful textbook (e.g., The Unborn Patient: The Art and Science of Fetal Therapy). As the number and quality of professionals devoted to fetal treatment increase, and the number of centers around the world continues to grow, the banner for fetal surgery in the 21st century should read: "Proceed with caution . . . and enthusiasm."

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Table 1. Milestones In Fetal Surgery		
Intrauterine transfusion (IUT) for Rh disease	(New Zealand)	1961
Hysterotomy for fetal vascular access - IUT	(Puerto Rico)	1964
Fetoscopy – diagnostic	(Yale)	1974
Experimental pathophysiology (Sheep)	(UCSF)	1980
Hysterotomy & maternal safety (Monkey)	(UCSF)	1981
Vesico-Amniotic shunt for uropathy	(UCSF)	1982
Vesico-Amniotic shunt for hydrocephalus	(Denver)	1982
Open fetal surgery for uropathy	(UCSF)	1983
Int'l Fetal Med & Surg Society founded	(Santa Barbara)	1982
CCAM resection	(UCSF)	1984
1st Ed., Unborn Patient: Prenatal Dx&Rx	(UCSF)	1984
Intravascular transfusion	(London)	1985
CDH open repair	(UCSF)	1989
Anomalous twin - cord ligation, RFA, etc.	(London)	1990
NIH Trial: Open repair CDH	(UCSF)	1990
Aortic valvuloplasty	(London)	1991
SCT resection	(UCSF)	1992
Laser ablation of placental vessels	(Milwaukee,London)	1995
EXIT procedure for airway obstruction	(UCSF)	1995
Fetoscopic surgery (Fetendo)	(UCSF)	1996
CDH – Fetendo clip → balloon	(UCSF)	1997
Myelomeningocele – open repair	(Vanderbilt)	1997
NIH Trial: Fetendo balloon CDH	(UCSF)	1998
Resection of pericardial teratoma	(UCSF)	2000
Resection of Cervical teratoma	(UCSF)	2001
NIH Trial: Open repair myelomeningocele	(UCSF,CHOP,Vanderbilt)	2002
NIH Trial: Twin-Twin Transfusion Syndrome	(CHOP,Perinatal Network)	2002

Table 2. Fetal Treatment 2002 Report Card

	Effect On Development	Report Card		Treatment	Report Card
		Patho-physiology	Selection		
Life-Threatening Defects					
Urethral obstruction	Hydronephrosis -> renal failure Lung hypoplasia -> pulmonary failure	B+	B	Percutaneous catheter Fetoscopic vesicostomy Open vesicostomy	B C C-
CCAM	Lung mass -> Fetal hydrops/ demise	B	B+	Open pulmonary lobectectomy	B
CDH	Lung hypoplasia -> Pulmonary failure	B	B-	Complete repair TTO: *Open* *Balloon*	C D C->A (Trial)
SCT	High output failure-> Fetal hydrops/ demise	B	B	Resect tumor Fetoscopic vasc occlusion Radiofrequency ablation	B C- C+
TTTS	Vascular steal thru placenta	C+	C	Open fetectomy Fetoscopic laser ablation of vessels Serial amnioreduction	D C->A (Trial) C->A (Trial)
Aqueductal Stenosis	Hydrocephalus	D	D	Ventriculo-amniotic shunt Open VP shunt	F D
Complete heart block	Low output failure	B	C	Open pacemaker Percutaneous pacemaker	D D
Pulmonary/Aortic stenosis	Outflow obstruction	C	C+	Valvuloplasty	D->B
Tracheal atresia/ stenosis	Overdistension by lung fluid			Tracheostomy Ex utero intrapartum Rx	C B-
Non-Lethal Defects					
Myelo-meningocele	Spinal cord damage	C+	B-	Fetoscopic coverage Open repair	D C->A (Trial)
Cleft lip/palate	Facial defect	C-	C-	Open repair	F
Metabolic Cellular Defects					
Stem cell/ enzyme defect	Hemoglobinopathy Immunodeficiency Storage disease	C	B	Stem cell transplant Gene therapy	C+ D
Predictable organ failure	Hypoplastic heart, kidney, lung	C	D	Induce tolerance for post-natal organ transplant	?

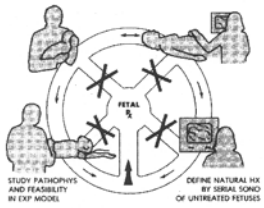
Table 3. Who Is The 'Surgeon' - Principles	
Operative "Team" With Broad Experience	
Perinatologists	
Pediatric Surgery Specialists	
Anesthesiologists	
Sonologists	
Nurses	
Technicians	
One Team Member Is Responsible For That Procedure	
	• Avoid 'Tag Team' surgery in which responsibility is handed off
'Surgeon' ∝ Best Outcome	
	•For closed, sonographically-guided needle and catheter shunts: Perinatologist/Sonologist >> Surgeon
	•For 'FETENDO' surgery requiring maternal laparotomy: Surgeon >> Perinatologist
	•For percutaneous fetoscopy: Perinatologist = Surgeon
	•For open complex repair: Surgeon >> Perinatologist

Table 4. Training Fetal Surgeons (Teams)		
	SURGERY	**PERINATOLOGY**
Residency	General Surgery – 5 yrs	OB/GYN – 4 yrs
Fellowship	Pediatric Surgery – 2 yrs	Perinatology/Genetics – 2 yrs
(?)Research	Laboratory – 2+ yrs	Laboratory – 2+ yrs
Credentials	American Board of Surgery	American Board of OB/GYN
Societies	♠ American College of Surgeons	♠ American College of OB/GYN
	♠ Specialty (APSA, *etc)*	♠ Specialty (SMFM, *etc)*
		• Int'l Fetal Medicine and Surgery Society

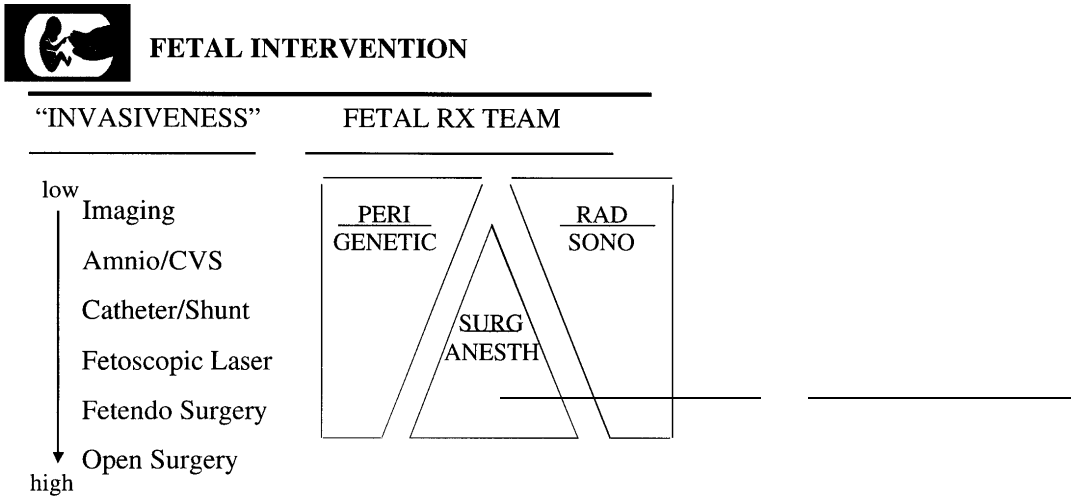
Table 5. Fetal Surgery Centers – How Many?			
Based on	**Resources Required Degree of Difficulty**		**to create**
Academic Multispecialty Model			3-10 Academic Centers
	e.g., UCSF, CHOP		
Perinatologist + Surgeon Model			10-30 Medical Centers
	e.g., Vanderbilt		
Virtuoso Model			Any hospital with virtuoso
	e.g., Tampa		
Based on Need – Number of "*Treatable*" Patients/Year In USA			
	♦ Surgery – CDH/CCAM/SCT	50-100/yr	1-2 per week
	♦ Surgery – MMC	100-200/yr	2-4 per week
	♦ Fetoscopy – TTTS, Misc	100-200/yr	2-4 per week
	♦ Catheter/Shunt – PUV, Effusions	100-200/yr	2-4 per week
		300-700/yr	7-14 per week

Harris Figure 1:

The impetus for fetal treatment came from pediatricians and surgeons frustrated by diseases that were difficult to correct or already uncorrectable at birth, and from obstetricians and sonographers who saw fetuses with potentially correctable defects before birth. However, before fetal treatment could be implemented, the pathophysiology of the disorder and the feasibility of repair had to be established experimentally, and the natural history of the diseases in the untreated human fetus had to be defined by serial sonography.



Harris Figure 2 – Fetal Intervention



Harris Figure 3